REMARKS

Applicants have amended Claim 1 to recite that the claimed antibody is isolated. Support for this amendment can be found, for example, at paragraph [0246] of the specification. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed July 6, 2005. For the reasons set forth below, Applicants respectfully traverse.

Priority Determination:

The PTO has stated that because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, Applicants are not entitled to the benefit of priority to any earlier filed application. However, for the reasons set forth below, the instant application and the priority applications do meet the requirements of 35 U.S.C. § 112, first paragraph, and therefore, are entitled to an earlier priority date.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to U.S. Provisional Application 60/105881 filed 10/27/1998."

The sequences of SEQ ID NOs: 81 and 82 were first disclosed in U.S. Provisional Application 60/105,881 filed 10/27/1998 as SEQ ID NO:1 and 2 and in Figures 1 and 2. These same sequences were disclosed in PCT/US99/20111 and in 09/403,297 as SEQ ID NO:141 and 142, Figures 85 and 86. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants maintain that the present application is fully entitled to the benefit of at least the priority date of August 24, 2000.

Rejection under 35 U.S.C. §101 – Utility

The PTO has maintained the rejection of Claims 1-5 as lacking a specific, substantial, and credible utility. The PTO argues that utilities asserted in the specification are not specific and substantial or well established. The PTO acknowledges that the nucleic acid encoding PRO1557 has utility, but, according to the PTO the claimed antibodies do not have utility. The PTO states, "[w]ere PRO1557 differently expressed, were this expression significant and repeatable and were the information sufficiently complete to allow use of the polypeptide without undue experimentation, it would have utility as a diagnostic tool. It, however, has none of these necessities." Office Action at 7.

The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO newly cites Haynes *et al.* (Electrophoresis 19:1862-1871 (1998)) and Fessler *et al.* (J. Biol. Chem. 277(35):31292-31302 (2002)) to support its assertion that protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript.

Applicants respectfully disagree and submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility.

Finality of the Rejection is Premature

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking utility, stating that the reasons are set forth in the previous Office Action. In the present Office Action, the PTO states, "For reasons discussed at length in the previous Office action, even if the encoding polynucleotide has utility, on [sic] cannot on that basis alone support a utility for the encoded protein or antibody because the prior art provides sufficient support to make a correlation between mRNA and encoded protein level unpredictable (*e.g.*, Haynes et al., Electrophor. 1998, previously cited)" (Office Action at 2-3). However, Haynes et al. was not previously cited, and the previous Office Action made no assertion that prior art suggests protein levels are unpredictable from mRNA. Thus, instead of relying on previously presented evidence and arguments, the PTO has adopted new arguments, and has cited two new references for support. Because the PTO has presented new arguments and evidence, and is making assertions

of fact not relied on in the previous Office Action, Applicants submit that the finality of the present rejection is improper. M.P.E.P. § 706.07 makes this point clear:

> Before final rejection is in order a clear issue should be developed between the examiner and applicant. ... Switching from one subject matter to another in the claims presented by applicant in successive amendments, or from one set of references to another by the examiner in rejecting in successive actions claims of substantially the same subject matter, will alike tend to defeat attaining the goal of reaching a clearly defined issue for an early termination, i.e., either an allowance of the application or a final rejection. ... The applicant ... should receive the cooperation of the examiner ... and not be prematurely cut off in the prosecution of his or her application. ... The examiner should never lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and that a clear issue between applicant and examiner should be developed, if possible, before appeal.

Because the PTO is relying on new references and new arguments, Applicants should be given the opportunity to submit references and arguments in response. Finality is improper because a clear issue has not been developed for Appeal until Applicants have had an opportunity to place their arguments and supporting documents in the record. Applicants therefore request that the finality of the rejection be withdrawn, or at a minimum, that the arguments and references cited herein be entered into the record for purposes of appeal.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations

used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to

> convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> *[I]n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a

"significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly esophageal and kidney cancer. Applicants are not asserting that the claimed antibodies necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1557 polypeptide is more highly expressed in esophageal tumor tissue and kidney tumor tissue compared to normal esophageal tissue and normal kidney tumor, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1557 polypeptide is increased in esophageal tumor and kidney tumor, compared to normal esophageal tissue and normal kidney tissue, it is likely that the PRO1557 polypeptide is differentially expressed in

esophageal tumor and kidney tumor and therefore antibodies to the PRO1557 polypeptide are useful as a diagnostic tool to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO cites Hu *et al.*, Haynes *et al.* and Fessler *et al.* to support the position that there was no correlation between altered gene expression and a known role in a disease for genes displaying a 5-fold or less change in expression, and that mRNA levels are not predictive of protein levels;

2. The PTO asserts that the specification does not teach that the encoded polypeptide was differently expressed such that the expression was significant and repeatable, and does not teach information sufficiently complete to allow use of the polypeptide without undue experimentation.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, because Applicants have submitted evidence demonstrating that there is a well-established correlation between a change in the level of mRNA and a corresponding change in the levels of the encoded protein, the PRO1557 protein is likely differentially expressed in certain tumors. Second, this likely differential expression of the PRO1557 protein in certain tumors provides utility for antibodies to the PRO1557 proteins as cancer diagnostic tools. Third, the references provided by the PTO are not contrary to Applicants' arguments and evidence, and therefore do not support the PTO's position.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.**

The Gene Encoding the PRO1557 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

As a preliminary matter, Applicants address the PTO's position on the utility of nucleic acids encoding the PRO1557 polypeptide (e.g., SEQ ID NO:81). The Office Action, at page 10, states "it is agreed that the polynucleotide of SEQ ID NO:81 has this specific utility." Further, the utility of these nucleic acids has been recognized by the PTO in co-pending, co-owned patent application Serial No. 10/063,713 (drawn to nucleic acids relating to SEQ ID NO:81). Accordingly, Applicants presume that the utility of nucleic acids encoding the PRO1557 polypeptide is established, and, therefore, the differential expression data presented in Example 18 of Applicants' specification is no longer in question for purposes of utility determination.

In view of the PTO's recognition of the utility of nucleic acids encoding the PRO1557 polypeptide, Applicants submit that it is moot to respond statements in the present Office Action that question the differential expression of the nucleic acid, such as "Because as previously discussed there is critical information lacking which includes: whether differences in nucleic acid expression of PRO1557 were significant, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumor and normal control, the skilled artisan cannot use (whether in vivo or in vitro) the claimed invention." Office Action at 5. Thus, for purposes of this response, Applicants presume that the PTO no longer questions the differential expression of the PRO1557 nucleic acid as provided in Example 18.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants turn to their argument that it is well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO1557 polypeptide in esophageal tumor and kidney tumor, and given the knowledge in the art, it is likely that the PRO1557 polypeptide is differentially expressed; and antibodies specific for proteins differentially expressed in certain tumors have utility as diagnostic tools.

The PTO states that "there is influential art of record that requires the Examiner maintain that as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SE ID NO:81 positively correlates with the expression of the protein of SEQ ID

NO:82." For support of this assertion, the PTO cites the previously cited reference by Hu *et al.*, and the PTO also newly cites references by Haynes *et al.* and Fessler *et al.*

The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) as disclosing that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. Applicants respectfully submit that this reference does not satisfy the PTO's burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not less-prevalent ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression

levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease.

Applicants submit that a lack of known role for PRO1557 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1557 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

In response to Applicants earlier statements regarding Hu, the PTO states that the findings of Hu are suggestive of a correlation between expression level and activity. The PTO quotes the portion of Hu stating:

> It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful.

As the PTO has asserted, Hu studied differential gene expression and a *known* role in a disease. First Office Action at 3. Thus, Hu's analysis of differential expression of a gene whose role in a disease is "biologically meaningful" to the disease is completely different from Applicants' asserted differential expression of a gene for diagnostic purposes. Even if a gene does not have a meaningful role in causing a disease, this does not indicate that the gene does not show a consistent and measurable change in expression in the cancer. Whether or not a differentially expressed gene has a biologically meaningful role in a disease does not change the fact that differential expression of a gene and encoded polypeptide can be used in diagnosis of a disease. The lack of a biologically meaningful role of PRO1557 in cancer, for example, is

irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1557 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer and antibodies that bind the proteins have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See, e.g.,* previously-submitted U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, and also U.S. Patent No. 6,156,500 and U.S. Patent No. 6,562,343 attached hereto as Exhibits 1-2.).

Further, as noted in the previous section, the utility of the nucleic acid encoding the PRO1557 polypeptide is accepted by the PTO. Thus, insofar as the PTO is using Hu to challenge the utility of the claimed antibodies by questioning the validity of Applicants data regarding differential expression of the nucleic acid encoding the PRO1557 polypeptide, this point is now moot. In this regard, the PTO also discusses a reference by Wu *et al.* (Gene 311:105-110 (2003)). Wu reports measurements of mRNA of BNF-1 in normal and tumor tissues. Since the utility of the nucleic acid encoding the PRO1557 polypeptide is now accepted by the PTO, issues relating to this reference are now moot.

The PTO also asserts that polypeptide levels cannot be accurately predicted from mRNA levels, basing this assertion on the newly cited publication by Haynes *et al.* For the reasons discussed below, the Haynes *et al.* is not contrary to Applicants' asserted utility.

Haynes *et al.* studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state

transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels (Fig. 1)." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 3 (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Considering that Example 18 of the specification shows over-expression of PRO1557 mRNA in esophageal and kidney tumors, Haynes and Gygi actually provide strong evidence in support of a general correlation between mRNA and protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did <u>not</u> say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the <u>same</u> gene leads to an increase or decrease for the corresponding protein. Haynes did <u>not</u> study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

The PTO also newly cites the publication by Fessler *et al.* For the reasons discussed below, Fessler is not contrary to Applicants' asserted utility. Applicants submit that, if anything, Fessler supports Applicants' assertions in support of utility of the claim antibodies.

Applicants submit that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Applicants make no assertions regarding changes in protein levels when mRNA levels are unchanged, nor does evidence of changes in protein levels when mRNA levels are unchanged have any relevance to Applicants' assertion.

Fessler *et al.* studied changes in neutrophil (PMN) gene transcription and protein expression following lipoplysaccharide (LPS) exposure. Fessler lists in Table VIII a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of the 13 up-regulated proteins, a change in mRNA levels is reported for only 3 such proteins. For these 3, mRNA levels are increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels also are decreased. Thus, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Regarding the remainder of the proteins listed in Table VIII, in 6 instances, protein levels changed while mRNA levels were unchanged. This evidence has no relevance to Applicants' assertions of the influence that changes in mRNA levels have on protein levels. In explaining these instances, Fessler explains that LPS has post-transcriptional activity that can influence protein levels (Fessler at 31300, right column). Nothing in these results by Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results are not contrary to Applicants assertions.

In the remaining 6 instances listed in Table VIII, protein levels changed while mRNA was noted as "absent." This evidence also has no relevance to Applicants' assertions of the influence that changes in mRNA levels has on protein levels. By virtue of being "absent," it is not possible to tell whether mRNA levels were increased or decreased in PMN upon contact with LPS. Regarding these instances, Fessler explained that LPS may have post-translational activity that

can result in increased protein stability (Fessler at 31300, right column). Nothing in these results by Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results also are not contrary to Applicants assertions.

The PTO points to Fessler's statement regarding Table VIII that "a poor correlation was found between corresponding transcripts and proteins." (Fessler at 31300, right column). As is clear from the above discussion, this statement does not relate to a lack of correlation of a change in mRNA levels and protein levels, because in 5 of 6 such instances, changes in mRNA and protein levels correlated well. Instead, this statement relates to observations in which protein levels changed when mRNA was either unchanged or absent. As such, this statement is an observation that in addition to transcriptional activity, LPS also has post-transcriptional and possibly post-translational activity that affect protein levels. Thus, Fessler's results suggest that LPS has a transcriptional activity that can cause changes in protein levels which correlate with changes in mRNA levels, and LPS also has post-transcriptional activity that can cause changes in protein levels that do not correlate with unchanged or absent mRNA levels. Accordingly, Fessler's results are consistent with Applicants assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Even if Fessler's results had shown that a change in the level of mRNA did not generally lead to a corresponding change in the level of the encoded protein, which they did not, the accuracy of Fessler's results is uncertain. Fessler admits that there were "limitations" to the results reported. These limitations included: possible artifactual transcript-protein discordance due to a 4 hour delay in harvesting after LPS exposure; uncertain post-incubation but pre-electrophoresis effects on protein synthesis, degranulation and exocytosis; and limited ability to quantitate protein amounts using Coomassie Blue. (Fessler at 31301, left column). Fessler exemplifies one such spurious result, in which there was a disparity between observed increase in cytokine mRNA, but an absence of detected cytokine proteins, which, as Fessler explains, "reflects their removal in the post-LPS incubation wash." (Fessler at 31297, right column). Thus, Fessler acknowledges "limitations" to the conclusion that, for some genes, transcript levels did not coincide well with corresponding protein levels, leaving it uncertain the extent to which actual changes in protein levels differed from mRNA levels when neutrophils were exposed to LPS. As such, Fessler does not represent "influential art ... that requires the Examiner maintain

that as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:81 positively correlates with the expression of the protein of SEQ ID NO:82." (Office Action at 5). Instead, Fessler represents a teaching that LPS might cause transcriptional changes that correlate with changes in protein levels, and might also cause post-transcriptional changes in protein levels when mRNA levels are unchanged. Accordingly, Fessler is not contrary to Applicants' asserted utility.

In view of the above, none of Hu, Haynes or Fessler is contrary to the assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Furthermore, Applicants have submitted evidence that changes in mRNA are positively correlated to changes in protein levels. For example, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are

predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the previously-submitted teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002)). Figure 9-2 of Alberts 3rd ed. shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Alberts 3rd ed. provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Alberts 3rd ed. at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Alberts 3rd ed. at 453 (emphasis added). Thus, as established in Alberts 3rd ed., the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Alberts 4th ed., Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Alberts 4th ed. at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Alberts 4th ed. illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Alberts 4th ed. at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Alberts 4th ed. at 379 (emphasis added).

Further support for Applicants' position can be found in the previously-submitted textbook excerpt from Genes VI, (Benjamin Lewin, Genes VI (1997)) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming

majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in the previously submitted publication by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression." Zhigang at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Zhigang at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Zhigang at 7.

Further, the previously submitted publication by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. In light of the lack of support by the cited references for the PTO's argument to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1557 mRNA is expressed at a higher level in esophageal tumor and kidney tumor compared to normal esophageal and normal kidney tissue, respectively, the PRO1557 polypeptide will have the same expression pattern. This differential

expression of PRO1557 and related polypeptides make antibodies specific for such polypeptides useful as diagnostic tools for cancer.

The PTO dismisses the declarations and publications submitted by Applicants because the specification fails to provide sufficient information such as "expression level range for normal and tumor tissues, specific types of kidney or esophageal tumors detectable, and probability of detection for any particular kidney or esophageal tumor type (*e.g.*, whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested), or if and how much the PRO1557 polypeptide is expressed in normal *versus* tumor kidney and esophageal tissue." Office Action at 7, emphasis in original. Thus, the PTO appears to take the position that additional data and evidence, beyond the evidence already provided in the specification at Example 18 and the evidence already presented in the Declarations and other exhibits, must be disclosed in order for Applicants to initially establish a utility for the claimed antibodies. Applicants submit that the PTO's prerequisite of additional evidence is beyond that necessary to establish utility.

Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. See *In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); M.P.E.P. §2107.02 (III). Requests for additional evidence should be imposed rarely, such as only when a statement is incredible in the light of the knowledge of the art, or factually misleading. *In re Citron*, 325 F.2d 248, 139 USPQ 516 (CCPA 1963); M.P.E.P. §2107.02 (V). In the instant case, the volume of additional evidence to meet a threshold of initially establishing utility as laid out by the PTO goes well beyond a request for evidence to clarify or support an incredible or misleading statement. Even for inventions claiming a pharmacological or therapeutic utility, the Federal courts have consistently reversed rejections by the PTO asserting a lack of utility where an applicant has provided evidence supporting the utility. M.P.E.P. §2107.03. Applicants have provided evidence in both Example 18 and the Declarations and other exhibits that describe the assay methods and interpretation of results, and demonstrate the correlation between changes in mRNA and protein levels as detailed above. Thus, Applicants have provided a variety of evidence supporting the utility of the claimed antibodies. Accordingly, the requirement for Applicants to provide additional evidence is improper.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

As discussed above, the PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed antibodies can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly esophageal and kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO1557. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1557 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene encoding the PRO1557 polypeptide is expressed at least two-fold higher in esophageal tumor tissue and kidney tumor tissue compared to normal esophageal tissue and normal kidney tissue, respectively. These data are strong evidence that the PRO1557 gene and polypeptide are associated with esophageal and kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1557 gene and polypeptide with two specific diseases. Use of the claimed antibodies a diagnostic tool for cancer, particularly esophageal tumor and kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue and the literature teaches that mRNA levels are not predictive of protein levels; and (2) the specification does not teach that the encoded polypeptide was differently expressed such that the expression was significant and repeatable, and does not teach information sufficiently complete to allow use of the polypeptide without undue experimentation. Applicants have addressed each of these arguments in turn.

First, the Applicants have shown that the Hu *et al.* reference cited by the PTO does not teach that genes differentially expressed in cancer cannot be used as diagnostic tools. In fact, Hu does not address this issue, either directly or indirectly, and therefore does offer no support for

the PTO's position. Further, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. Neither Haynes *et al.*, nor Fessler *et al.* are contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question these declarations and supporting references.

Second, Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. Applicants submit that the Declaration and references cited by Applicants above demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The references offered by the PTO do not support a position to the contrary. Therefore, one of skill in the art will recognize that the PRO1557 polypeptides are differentially expressed in tumor relative to normal tissue, and, as such, the antibodies that specifically bind the PRO1557 antibodies have utility as diagnostic tools for cancer.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1557 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a

whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1557 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO rejected Claims 1-5 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled. The PTO also states that undue experimentation would be required to use the claimed antibodies.

Applicants respectfully traverse.

Applicants submit that, insofar as the rejection under 35 U.S.C. § 112, first paragraph, is based on the PTO's holding of a lack of utility, Applicants have established in the discussion of the 35 U.S.C. § 101 rejection above, a substantial, specific, and credible utility for the claimed antibodies. Accordingly, Applicants submit that the claimed antibodies have a utility and, therefore, should not be rejected under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Insofar as the rejection under 35 U.S.C. § 112, first paragraph is based on conclusion of a lack of enablement separate from the PTO's finding of a lack of utility, Applicants submit that one skilled in the art could have made and used the claimed antibodies without undue experimentation. The PTO evaluates the invention in the light of factors to be considered for enablement (herein referred to as "Wands factors") in asserting that the claimed antibodies cannot be used without undue experimentation. The PTO does not appear to assert that the claimed antibodies cannot be made. Accordingly, Applicants address only whether or not one skilled in the art could have used the claimed antibodies without undue experimentation.

The PTO considers several Wands factors in concluding that the claimed antibodies lack enablement. The PTO acknowledges that the breadth of the claims is not an issue, but asserts that the nature of the invention, the state of the prior art, the skill in the art, and the direction in the specification indicate that the claimed antibodies could not be used without undue

experimentation. Regarding the nature of the invention, the state of the prior art, and the skill in the art, the PTO emphasizes that since the PRO1557 protein was unknown in the art, details of the expression of the protein were unknown. Regarding the direction in the specification, the PTO finds this insufficient because "the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened." Office Action at 4.

Applicants respectfully submit that one skilled in the art could have readily used the claimed antibodies. Regarding the state of and level of skill in the art, Applicants submit that one skilled in the art could have readily used an antibody that specifically binds to the recited polypeptide. Ten years before the filing of Applicants' earliest priority document, the Court of Appeals for the Federal Circuit recognized that there was "a high level of skill in the art" of making and using antibodies and "all of the methods needed to practice the invention were well known." *In re Wands* 858 F.2d 731, 740, 8 USPQ2d 1400, 1406. Accordingly, it is not credible to conclude that one skilled in the art did not know how to use an antibody to the recited polypeptide.

Regarding the direction provided by the specification, Applicants teach at paragraph [0407] how to use the claimed antibodies:

> The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, *e.g.*, detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I, a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

Further, in Example 18, Applicants identified particular organs in which the nucleic acid encoding PRO1557 is overexpressed when tumorous. Thus, the specification teaches one skilled in art particular methods to employ and particular organs to target in using the claimed antibodies. Therefore, the specification taught one skilled in the art to use the claimed antibodies to specifically bind the PRO1557 polypeptide in kidney and esophagus samples. Since it was routine in the art to use antibodies for polypeptide detection, one skilled in the art would need no more than routine experimentation to use the claimed antibodies to specifically bind the PRO1557 polypeptide in kidney and esophagus samples.

The PTO indicates that the specification is insufficient because the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP §2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Based on the teachings of the specification and the level of skill in the art, it was routine to use antibodies such as the claimed antibodies, and one skilled in the art knew which particular organs to target for detection with the antibodies. No undue experimentation was required for a Ph.D. scientist with several years of experience to use these routine methods, in view of the teachings in the specification, in order to determine details such as the exact location of the PRO1557 polypeptide or to determine specific details of differential expression between normal and tumor. Accordingly, it would not have required undue experimentation for one skilled in the art to make and use the claimed antibodies. The claimed invention is, therefore, fully enabled.

In view of the above, Applicants request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO has rejected Claims 1-5 as anticipated under 35 U.S.C. §102(b) by WO 00/70049. The PTO states that WO 00/70049 teaches a protein sequence that is 100% identical to Applicants' SEQ ID NO: 82, and antibodies specific thereto. As discussed above, the instant claimed subject matter has utility based upon the data in Example 18 and the instant application is a continuation of PCT/US00/23328; therefore, the present claims are entitled to the filing date of August 24, 2000. WO 00/70049 is not prior art under § 102(b).

WO 00/70049 was published on November 23, 2000, which is subsequent to the filing of priority application PCT/US00/23328 (August 24, 2000). Again, PCT/US00/23328 discloses the differential expression data which provides utility for the instant claims, and Applicants are entitled to the filing date of August 24, 2000. Therefore, WO 00/70049 cannot be cited under § 102(b).

In view of the above discussion, reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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